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# *Platycodi radix* beverage ameliorates postprandial lipemia response through lipid clearance of triglyceride-rich lipoprotein: A randomized controlled study in healthy subjects with a high-fat load

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**BACKGROUND/OBJECTIVES:** Elevation of postprandial lipemia characterized by a rise in triglyceride (TG)-rich lipoproteins can increase the risk of atherogenesis. The objective of this study was to investigate postprandial lipemia response to a single dietary fat/sugar load test and monitor beneficial changes induced by the consumption of *Platycodi radix* (AP) beverage in healthy subjects.
**SUBJECTS/METHODS:** A total of 52 subjects were randomly assigned to either placebo or AP beverage group with a high-fat shake in a randomized controlled crossover trial. Postprandial blood was collected at 0, 1, 2, 4, and 6 h and analyzed for TG and lipoprotein lipase mass. Inhibition of pancreatic lipase was determined *in vitro*.
**RESULTS:** AP inhibited pancreatic lipase activity *in vitro* ($IC_{50}$ = 5 mg/mL). Compared to placebo beverage, AP beverage consumption with a high-fat shake induced significant increase of plasma lipoprotein lipase mass ($P$ = 0.0111, β estimate = 4.2948) with significant reduction in very low-density lipoprotein (VLDL) TG concentration ($P$ = 0.038, β estimate = -52.69) at 6 h. Based on significant correlation between high-fat dietary scores MEDFICTS and postprandial TG responses in VLDL ($P$ = 0.0395, r = 0.2127), subgroup analysis revealed that 6 h-postprandial VLDL TG response was significantly decreased by AP consumption in subjects with MEDFICTS ≥ 40 ($P$ = 0.0291, β estimate = -7214).
**CONCLUSIONS:** AP beverage might have potential to alleviate postprandial lipemia through inhibiting pancreatic lipase activity and elevating lipoprotein lipase mass. Subgroup analysis revealed that subjects with high-fat dietary pattern could be classified as responders to AP beverage among all subjects.

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**Keywords**: *Platycodi radix,* postprandial lipemia, pancreatic lipase, randomized controlled trial

## INTRODUCTION

Prolonged elevation of triglyceride (TG)-rich lipoprotein level during postprandial lipemia is recognized as an important risk factor for cardiovascular disease (CVD) [1]. In a large prospective cohort of initially healthy women, Bansal *et al*. [2] have demonstrated that postprandial TG concentration is a better predictor for CVD than fasting TG concentration. In mechanistic studies using healthy normolipidemic subjects, dietary lipids are packed into chylomicrons after absorption in the small intestine, transferred into the blood, and converted to very low-density lipoprotein (VLDL) in the liver. Therefore, postprandial lipemia is a result of an increase in both intestine-derived chylomicrons and liver-derived VLDL [3]. Various non-modifiable factors (genetic factors, age, gender, and pathological conditions) and modifiable life style choices determine the rate of digestion, absorption, incorporation into the blood stream, and excretion of dietary lipids. Modifiable factors include physical activity, smoking, alcohol, medication, and dietary choices [4].

The balloon flower (*Platycodon grandiflorum*) is a perennial plant of the Campanulaccae family. Its roots *Platycodi radix* are commonly known as doraji in South Korea, jiegeng in China, and kikyo in Japan [5]. They have been traditionally used as a remedy for cough, cod, bronchitis, asthma, and sore throat [6]. Previous *in vitro* and *in vivo* (animal) studies have shown that *Platycodi radix* can reduce the elevation of blood TG levels in high-fat diet-fed mice due to inhibition of intestinal absorption of dietary fat [7,8]. Zhao *et al*. [9] have also demonstrated that platycodin D, a bioactive component from *Platycodi radix*, can decrease serum TG concentration, but increase fecal TG excretion

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in Institute of Cancer Research (ICR) mice, suggesting that *Platycodi radix* has anti-atherogenic potential. These findings triggered us to extend our studies to humans using aqueous extract of *Platycodi radix* (AP).

In this study, we hypothesized that a beverage made of AP may be useful as an effective tool to alleviate postprandial hyperlipidemia encountered in daily life. To investigate this hypothesis, we conducted a randomized double-blinded, placebo-controlled crossover trial and monitored the impacts of AP beverage on modifying postprandial TG levels in intestine-derived chylomicrons and liver-derived VLDL for 6 h after challenging with a standardized high-fat shake in healthy normolipidemic subjects. The impacts of AP beverage on pancreatic lipase activity *in vitro* and lipoprotein lipase level in plasma were also determined. Furthermore, we investigated whether dietary habits can discriminate responders from non-responders among subjects with AP beverage. To the best of our knowledge, this is the first study that assesses the inhibiting effect of AP on postprandial lipemia in a randomized clinical trial.

## SUBJECTS AND METHODS

*Study materials*

AP and placebo beverages were kindly provided by Chunho Food (Busan, Korea). Briefly, *Platycodi radix* was extracted by pressurized hot-water (3:10) at 120°C and 1.8-2 bar for 3 h, concentrated (75 ± 5°C, 20-70 cmHg, 2 h) to make 6.5 wt% solid content, filtered, and sterilized. AP beverage packed in an 80 mL pouch contained 100% AP. The placebo beverage contained 2.3% flavors and 97.7% purified water to provide similar taste, color, and flavor as AP beverage.

*Subjects and study design*

The study protocol was reviewed and approved by the Institutional Review Boards (IRB) of Ewha Womans University. This study was registered in the WHO International Clinical Trials Registry Platform with the following identification number: KCT0002296. Subjects between ages of 20 and 40 were recruited through online and poster advertisements. Subjects were excluded if they met the following criteria: weight change > 10% in the previous 6 months; body mass index (BMI) < 18.5 or > 30.0 kg/m$^2$; medication and/or dietary supplement use in the previous month; smoking > 1 pack per day; drinking > 140 g per week; history of liver diseases, kidney disease, diabetes, or cardiovascular disease (hypertension or stroke); and pregnancy or lactation.

A total 52 eligible subjects were enrolled in the trial after obtaining written informed consent. They were randomly assigned to placebo or AP group in a randomized fashion. Following a one-week wash-out period, subjects were switched to the alternative group for another session. Each session was begun by providing participants with a standardized high-fat shake (total 900 kcal; 58.9% energy from fat, 33.3% energy from carbohydrate, and 7.6% energy from protein) and each test beverage. This standardized high-fat shake contains 60 g palm oil and additional sugar and protein (83.5 g dextrose, 20 g protein powder), and 336.5 mL water. Subjects were instructed to consume one of the 80 mL beverages right after consumption of a standardized high-fat shake without water within 5 min. Participants were asked to maintain usual diet, but refrain from *Platycodi radix* and saponin-containing foods during the experimental period. The same dinner was provided on the day before the intervention. Each session began at 9 am in the morning with collection of fasting blood into ethylenediamin-detetraacetic acid (EDTA) tubes (BD Biosciences, San Jose, CA, USA). Postprandial blood samples were then collected at 1, 2, 4, and 6 h after ingestion of the high-fat shake and test beverage.

*Assessment of habitual dietary patterns*

Antioxidant dietary patterns of whole grain, legumes, vegetables, fruits, fish, dairy products, nuts, and tea were assessed by Recommended Food Score (RFS). RFS scores ≥ 36 out of 47 was identified as a high quality diet [10]. High-fat dietary patterns of meats, eggs, dairy, frying foods, baked goods, convenience foods, table fats, and snack were assessed by MEDFICTS questionnaire. Scores were classified as low (< 40), moderate (40-69), and high (≥ 70).

*Separation of chylomicron and VLDL fractions*

Blood samples were centrifuged within 20 min of collection at 1,500 g for 10 minutes at 4°C to obtain plasma. Chylomicrons and VLDL were isolated by salt density gradient ultracentrifugation at 40,500 g for 30 min at 16°C according to the method of Redgrave and Carlson [11]. We used ultracentrifuge (Beckman-Coulter Inc., Fullerton, CA, USA) with 50.4 Ti rotor at 19°C to separate two fractions: chylomicron at 40,500 g for 30 min and VLDL at 153,000 g for 16 h.

*Determination of TG concentration*

TG concentrations in plasma, and chylomicron and VLDL fractions were measured enzymatically using Roche-Hitachi Cobas 8,000 c702 chemistry autoanalyzer (Roche Diagnostics, Mannheim, Germany).

*Determination of pancreatic lipase activity*

Inhibitory activity of AP on pancreatic lipase activity was determined by measuring the amount of oleic acid released from triolein by adapting the method of Xu *et al.* [12]. A suspension of triolein, phosphatidylcholine, lecithin, and taurocholic acid in 0.1 M N-tris-(hydroxymethyl)-methyl-2-aminoethanesulfonic acid buffer containing 0.1 M NaCl was sonicated for 5 min. Enzyme reaction was started by adding pancreatic lipase and various concentrations of sample solutions. After incubation at 37°C for 30 min, concentration of free acids in the reaction mixture was measured using oleic acid as the standard. Inhibitory activity was reported as the relative percentage compared to control value.

*Quantification of lipoprotein lipase in plasma*

Lipoprotein lipase (LPL) in plasma was quantified at 0 and 6 h using an enzyme immunoassay kit (Cell Biolab Inc., San Diego, CA, USA). Briefly, plasma samples were diluted in phosphate-buffered saline (PBS) containing 0.1% bovine serum albumin (BSA). An aliquot was added to anti-LPL antibody coated plate and incubated at 37°C for 2 h. After three washes and removal of excess water, biotinylated anti-LPL antibody was

added and incubated at room temperature for 1 h on an orbital shaker. After three washes, substrate solution was added to each well and incubated at room temperature for 2-30 min until color changed rapidly. The reaction was stopped by adding stop solution. Absorbance was read at wavelength of 450 nm on a spectrophotometer using a microplate reader (BioTek, Winooski, VT, USA).

*Statistics*

The minimum necessary sample size was estimated to be 26 subjects per group based on similar trials [13,14]. With this sample size and alpha (two-sided) of 0.05, the study would provide around 80% power allowing 25% of dropout.

Potential outliers were identified as observations exceeding 1.5 times the interquartile range (IQR): Q1-(1.5 × IQR) and Q3 + (1.5 × IQR). Baseline characteristics were assessed using Student's *t*-test. Response data are given as concentration peak plotted against time after correction by baseline value. Incremental areas under the curve (AUC), maximum concentration ($C_{max}$), and time to reach $C_{max}$ ($T_{max}$) were calculated as summary values. Stepwise multiple linear regression models were performed to investigate the association of each response variable with baseline variable and potential confounding variables were selected. Data were tested for normal distribution by means of quantile-quantile (QQ) plot. Group differences were estimated with a linear mixed-effects model, controlling for treatment, time, sequence, and period as fixed effects with subject as a random effect after adjusting for potential confounding variables (pulse, waist, weight, leukocyte, mean corpuscular hemoglobin concentration (MCHC), and MEDFICTS). Furthermore, we analyzed relationship between RFS/MEDFICTS and TG concentrations by using a Pearson correlation analysis for all groups. Sub-group analysis was conducted to explore the effect of habitual eating patterns on postprandial TG response in TG-rich lipoproteins using analysis of covariance (ANCOVA). Data are presented as means ± standard errors (SEs). Statistical analyses were performed using SAS program package version 9.4 (SAS Institute, Cary, NC, USA) and *P*-values < 0.05 were considered significant.

## RESULTS

A total of 52 eligible subjects were assigned to either placebo or AP group according to random allocation sequence. Eight subjects discontinued the study prematurely due to withdrawal of consent (n = 6), taking medication (n = 1), and personal reason (n = 1) (Fig. 1). There were no significant adverse effects of AP or placebo beverages. Characteristics for all subjects are summarized in Table 1. They were typically healthy adults with a mean age of 24.7 ± 0.3 years and a mean BMI of 22.5 ± 0.4 kg/m$^2$. They were in good health as determined by physical examination and routine blood and urine biochemical screening (data not shown). As intention-to-treat (ITT) and per-protocol (PP) data sets were identically evaluated in this study, only ITT data were reported.

**Table 1.** Baseline characteristics of participants

| Variable | Total (n = 52) | Normal range |
|---|---|---|
| Age (yrs) | 24.7 ± 0.3 | |
| Sex (male/female) | 26/26 | |
| Height (cm) | 169.2 ± 1.1 | |
| Weight (kg) | 64.8 ± 1.5 | |
| Body mass index (kg/m$^2$) | 22.5 ± 0.4 | |
| Waist circumference (cm) | 78.6 ± 1.1 | |
| Pulse rate (beats/min) | 84.7 ± 2.1 | 60-100 |
| Body temperature (℃) | 36.4 ± 0.0 | 35.8-38.0 |
| Blood pressure (mmHg) | | |
| Systolic blood pressure | 117.8 ± 1.7 | ≤ 120 |
| Diastolic blood pressure | 70.7 ± 1.2 | ≤ 80 |
| Cigarette smoker, n (%) | 8 (15.4%) | |
| Alcohol drinker, n (%) | 42 (80.8%) | |
| Physical activity (h/week) | 0.6 ± 0.2 | |
| RFS | 18.1 ± 1.3 | |
| MEDFICTS (low/moderate/high) | 17/23/7 | |

Values are expressed as means ± SE. RFS, Recommended food score; and MEDFICTS, meats, eggs, dairy, frying foods, baked goods, convenience foods, table fats, and snack.

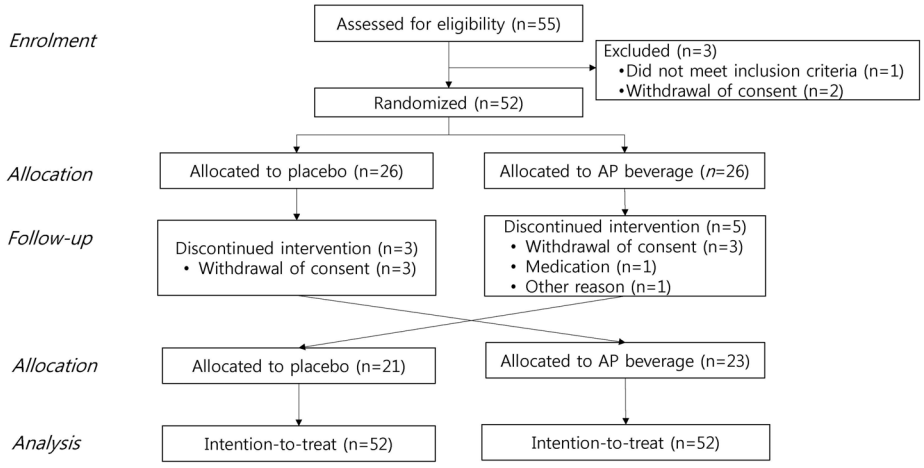


**Fig. 1.** CONSORT diagram illustrating the enrolment, group allocation, follow-up, and analysis of all subjects in this study. Fifty-two eligible subjects were randomly divided to one of the two groups, followed by over a week wash-out period and subsequent crossover to the alternate group. AP, aqueous extract of *Platycodi radix*.

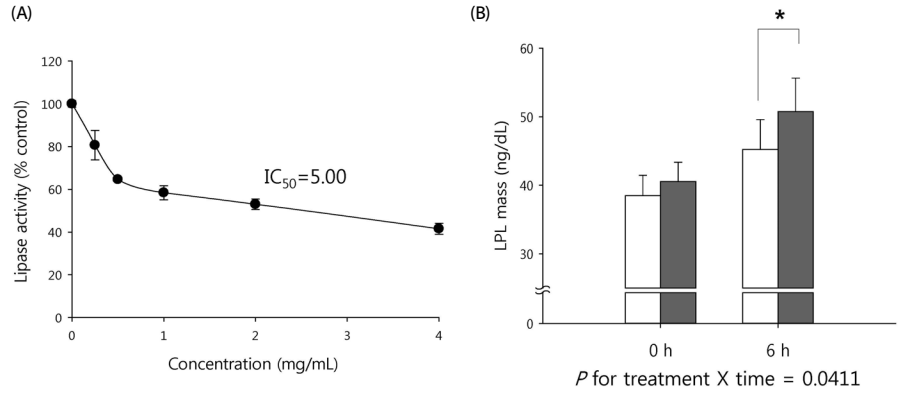


**Fig. 2.** Effect of AP on (A) *in vitro* inhibition of pancreatic lipase activity (n = 3) and (B) lipoprotein lipase level in healthy subjects receiving placebo (○) and AP (●) beverages with a high-fat shake (n = 52/group). AP, aqueous extract of *Platycodi radix*. Values are expressed as means ± SE. Statistical significance was determined using a Linear Mixed Effect Model controlled for potential confounding variables. * $P < 0.05$

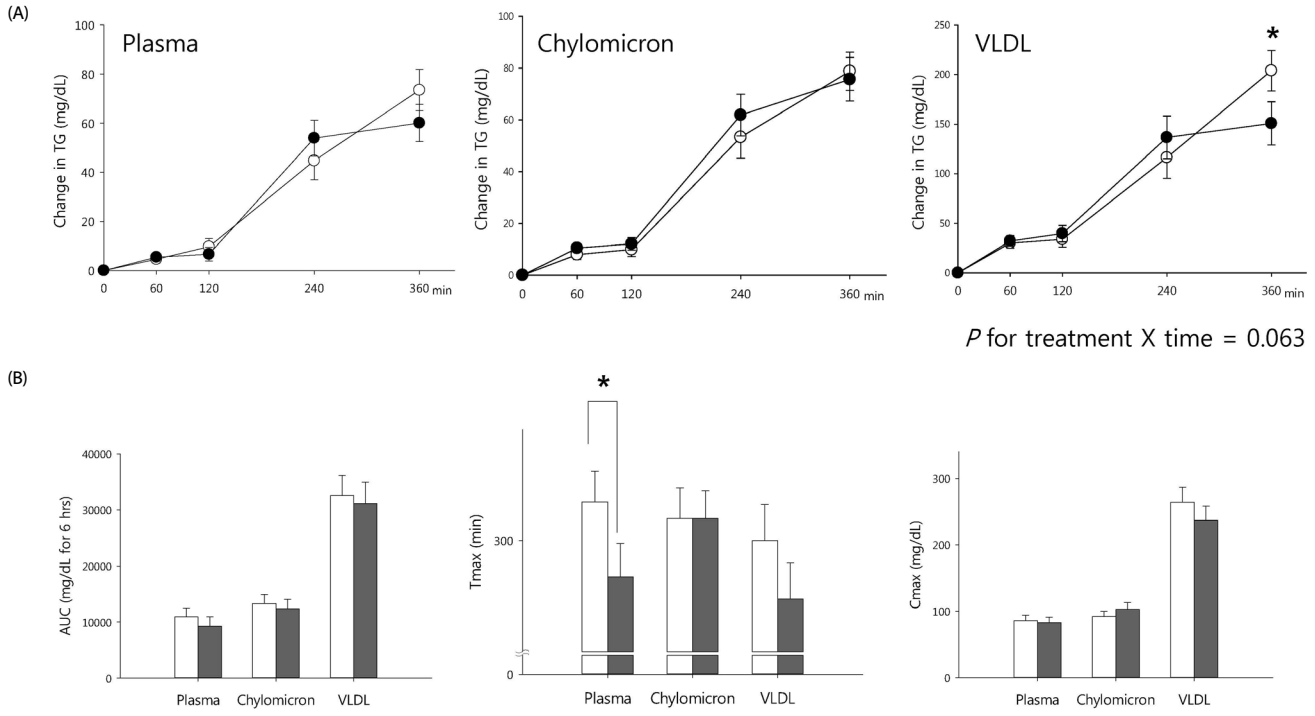


**Fig. 3.** Postprandial TG response in plasma, chylomicron fraction, and VLDL fraction in healthy subjects to placebo (○) and AP (●) beverages with a high-fat shake (n = 52/group): (A) Concentration-time profile, (B) Summary values. TG, triglycerides; VLDL, very-low density lipoprotein; AP, aqueous extract of *Platycodi radix*. Values are expressed as means ± SE. Statistical significance was determined using a Linear Mixed Effect Model controlled for potential confounding variables. * $P < 0.05$

*Effect of AP on pancreatic lipase activity and plasma lipoprotein lipase level*

AP inhibited pancreatic lipase activity in the assay system using triolein emulsified with phosphatidylcholine, lecithin, and taurocholic acid (Fig. 2A). $IC_{50}$ values of AP for inhibiting pancreatic lipase activity was 5 mg/mL. LPL mass was also determined in plasma at baseline and 6 h (Fig. 2B). Results demonstrated that there was a significant increase of LPL mass at 6 h in AP beverage group compared to that in the placebo beverage group ($P = 0.0111$, β estimate = 4.2948).

*Effect of AP beverage on postprandial lipemia*

Postprandial TG responses are shown in Fig. 3A. A high-fat shake caused a gradual increase of TG concentration in plasma and TG-rich lipoprotein fractions at 6 h. However, compared to placebo beverage, AP beverage showed a tendency of suppressing TG response during later time point in VLDL fraction ($P = 0.063$). Particularly, VLDL TG concentration was significantly lower at 6 h in AP beverage group compared to that in placebo beverage group ($P = 0.038$, β estimate = -52.69). Fig. 3B showed that incremental response area above baseline and $C_{max}$ did not differ significantly for the 6 h observation period, although AP beverage group generally showed lower

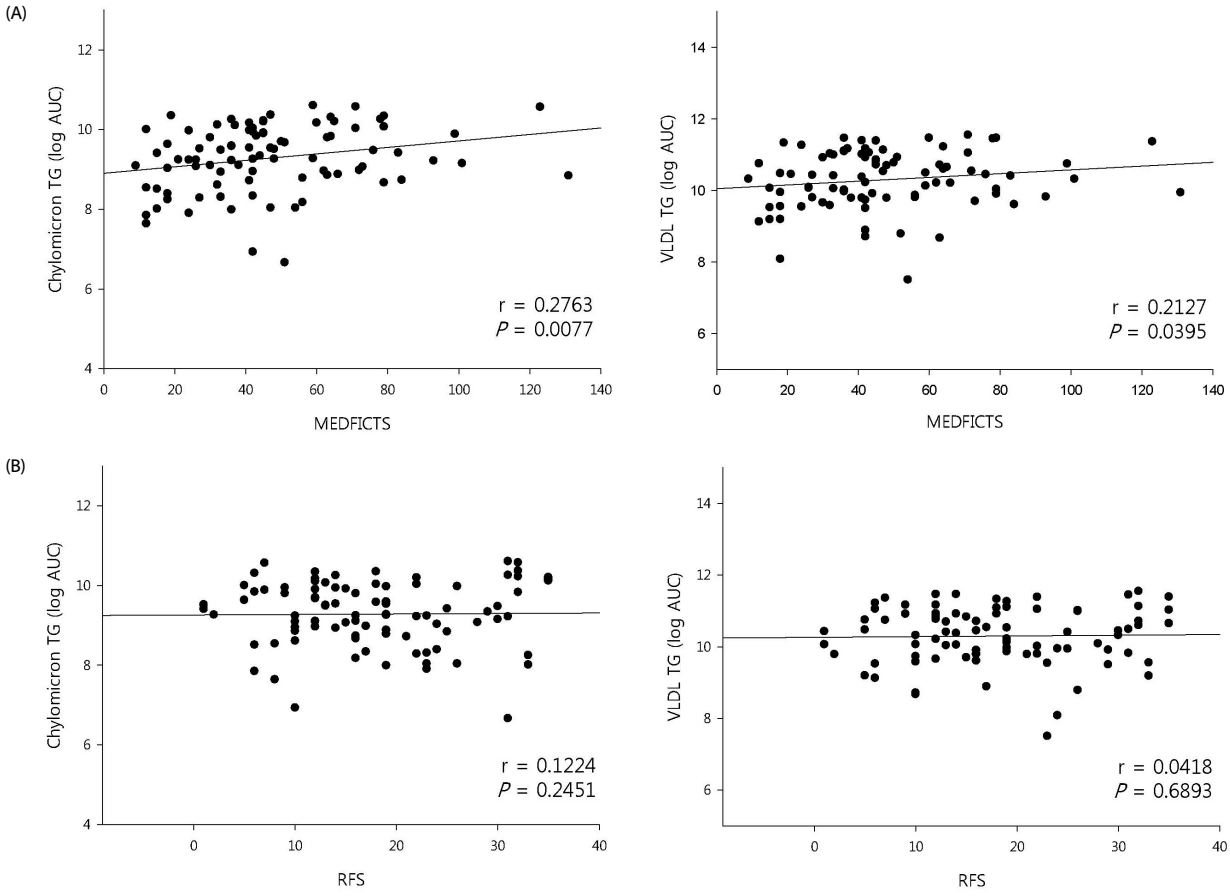


**Fig. 4.** Correlation between postprandial TG response (y axis) and (A) MEDFICTS and (B) RFS (x axis) in all subjects (n = 104). TG, triglycerides; MEDFICTS, meats, eggs, dairy, frying foods, baked goods, convenience foods, table fats, and snack; RFS, recommended food score. *P*-values and correlation coefficients shown in each panel were determined by Pearson correlation analysis. The solid line represents a regression line.

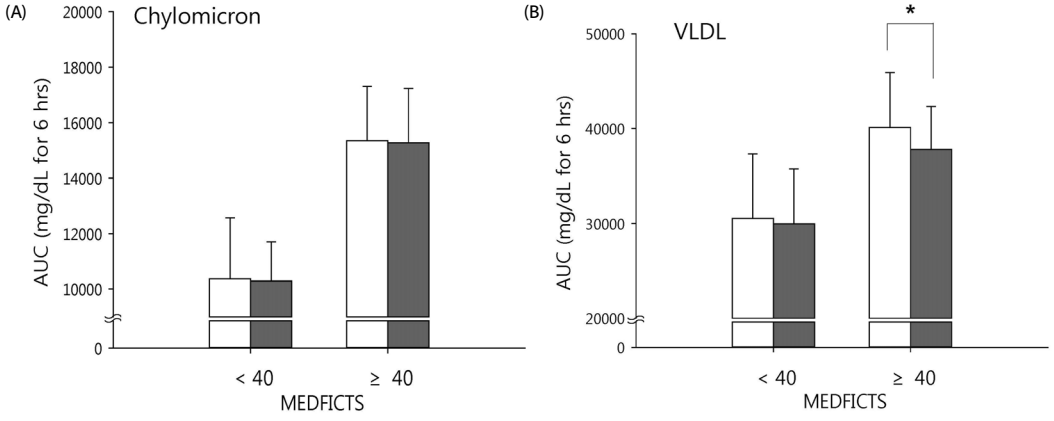


**Fig. 5.** Comparison of postprandial TG response in (A) chylomicron and (B) VLDL between different groups after subgrouping subjects into MEDFICTS < 40 (n = 22 for placebo ○, and n = 25 for AP ●) and MEDFICTS ≥ 40 (n = 30 for placebo, and n = 27 for AP). TG, triglycerides; VLDL, very low-density lipoprotein; MEDFICTS, meats, eggs, dairy, frying foods, baked goods, convenience foods, table fats, and snack; AP, aqueous extract of *Platycodi radix*. *P*-values were calculated using ANCOVA. * $P < 0.05$

values than the placebo beverage group. However, $T_{max}$ was significantly decreased in plasma in AP beverage group compared to that in placebo beverage group ($P = 0.0125$, β estimate = -24.73).

*Correlation between dietary habits and postprandial lipoprotein-TG responses and subgroup analysis*

In all subjects, a significant correlation was obtained between MEDFICTS and postprandial TG responses in chylomicron ($P = 0.0077$, r = 0.2763) and VLDL ($P = 0.0395$, r = 0.2127) as measured

by AUC (Fig. 4A). However, no correlation was found between RFS and postprandial TG responses in lipoproteins (Fig. 4B).

A subgroup analysis was followed by stratification of subjects by MEDFICTS, where MEDFICTS diet score < 40 indicated dietary intake of < 7% saturated fat and < 200 mg/dL cholesterol. Results indicated that a decrease of postprandial VLDL-TG response became evident by AP consumption compared to placebo group, when subjects were sub-grouped with MEDFICTS $\geq$ 40 ($P = 0.0291$, $\beta$ estimate = -7214, Fig. 5A). However, ANCOVA did not reveal any significant difference in chylomicron (Fig. 5B).

## DISCUSSION

To the best of our knowledge, this is the first paper investigating beneficial changes induced by consumption of AP beverage following a single dietary fat/sugar load in healthy subjects. We demonstrated that AP beverage had a potential to accelerate lipid clearance in TG-rich lipoproteins by inhibiting intestinal lipid absorption and facilitating lipoprotein lipase-mediated lipolysis. The involvement of lipases as possible targets of AP action was proved by determining its $IC_{50}$ value *in vitro* for inhibiting pancreatic lipase activity and lipoprotein lipase mass in plasma without heparin stimulation to reflect the *in vivo* lipolytic potential.

The postprandial state is a dynamic condition with rapid remodeling of lipoproteins [1]. The processes responsible for the clearance of postprandial TG include (1) chylomicron secretion by the intestine, (2) VLDL secretion by the liver, and (3) conversion of these TG-rich lipoproteins (chylomicron and VLDL) to TG-depleted lipoproteins (LDL, low density lipoprotein; and HDL, high density lipoprotein) and tissue uptake of TG-depleted lipoproteins [15]. Tissue uptake of TG-depleted lipoproteins is dependent on the expression of LDL receptor or LDL receptor related protein [16]. However, an acute effect on expression of these receptors seems unlikely in this 6 h response study. Therefore, in the present study, we focused on the fluctuation of TG levels in intestine-derived chylomicron as well as in liver-derived VLDL that might be attributed to pancreatic lipase and lipoprotein lipase.

Lipases are water-soluble enzymes that hydrolyze ester bonds of TG. They form a multigenic family that play different roles in the absorption and transport of lipid [17]. Pancreatic lipase plays a key role in the digestion of 50-70% of total dietary fats. The resulting lipolytic products are mixed with bile salts, carried to the intestinal enterocytes in the form of micelles, and secreted in chylomicron [12]. Therefore, inhibition of pancreatic lipase has been widely studied as a target mechanism for developing anti-hyperlipidemia and anti-obesity agents from natural botanical resources [18,19]. In support of our results, Han *et al*. [7,8] have reported that both crude AP extract and platycodin D, a signature component of AP, can inhibit pancreatic lipase activity *in vitro* and reduce blood TG elevation in rats. Zhao and Kim [20] have also reported inhibitory effect of platycodin D toward pancreatic lipase *in vitro* with detailed kinetic profiles and competitive inhibition, with Ki value of 0.18 $\pm$ 0.20 mM.

Lipoprotein lipase is well known as a primary enzyme required for the hydrolysis of TG in lipoproteins. Thus, its deficiency results in lipemic serum and hypertriglyceridemia [21]. Lipolysis is initiated when lipoprotein interacts with lipoprotein lipase which is bound on the luminal surface of the capillary endothelial cells via heparin sulfate proteoglycans. Of all lipoproteins, TG-rich lipoproteins (chylomicron and VLDL) have higher affinity for lipoprotein lipase than TG-depleted lipoproteins (LDL and HDL). Chylomicron and VLDL are known to share many common features. They compete for lipolysis by lipoprotein lipase. The remnants are cleared via liver LDL receptors and LDL receptor-related protein in muscle and adipose tissue [21]. Results of this study revealed that chylomicron and VLDL TG concentrations were significantly increased postprandially. However, the rate of TG increase in VLDL was significantly reduced at the later part of the response curve by consumption of AP beverage. In consistent with this result, we were able to show that lipoprotein mass was significantly increased at 6 h after AP beverage consumption compared to placebo beverage consumption, suggesting that an acceleration of TG clearance by AP beverage might be attributed to the increase of lipoprotein lipase mass.

Lastly, we analyzed the association between postprandial lipemia response and MEDFICTS (high-fat dietary pattern) or RFS (antioxidant dietary pattern) to evaluate whether habitual dietary pattern may give an impact on the modulatory effect of AP beverage for postprandial lipemia. RFS is a diet quality score developed and validated by our research group to quantify antioxidant dietary pattern [10]. MEDFICTS is a rapid dietary fat screener for assessing adherence to a diet in accordance with restriction for saturated fat and cholesterol recommendations [22]. As a result, we found that there was a significantly positive correlation between MEDFICTS and postprandial TG response in chylomicron and VLDL, i.e., the higher the MEDFICTS, the higher the TG AUC level. Subsequent analysis revealed that subjects with habitual dietary intake of $\geq$ 7% saturated fat and $\geq$ 200 mg/dL cholesterol (MEDFICTS $\geq$ 40) could be classified as responders to AP beverage.

This study has a limitation in that results were obtained from an acute response to single administration of AP beverage. However, the findings of this study are sufficient to suggest that AP beverage might have potential to alleviate postprandial lipemia through inhibiting pancreatic lipase and elevating lipoprotein lipase mass. Subjects who had a habitual high-fat dietary pattern showed higher postprandial lipemia response. Thus they could be classified as responder group to AP beverage. Additional clinical study is warranted to test the potential effect of long-term consumption of AP beverage on postprandial lipemia and endothelial function.

## CONFLICT OF INTEREST

The authors declare no potential conflicts of interests.

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